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In Vivo Neurobiological Effects of Ibogaine and Its O-Desmethyl Metabolite, 12-Hydroxyibogamine (Noribogaine), in Rats

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ABSTRACT

Ibogaine is a naturally occurring compound with purported antiaddictive properties. When administered to primates, ibogaine is rapidly o-demethylated to form the metabolite 12-hydroxyibogamine (noribogaine). Peak blood levels of noribogaine exceed those of ibogaine, and noribogaine persists in the bloodstream for at least 1 day. Very few studies have systematically evaluated the neurobiological effects of noribogaine in vivo. In the present series of experiments, we compared the effects of i.v. administration of ibogaine and noribogaine (1 and 10 mg/kg) on motor behaviors, stress hormones, and extracellular levels of dopamine (DA) and serotonin (5-HT) in the nucleus accumbens of male rats. Ibogaine caused dose-related increases in tremors, whereas noribogaine did not. Both ibogaine and noribogaine produced significant elevations in

plasma corticosterone and prolactin, but ibogaine was a more potent stimulator of corticosterone secretion. Neither drug altered extracellular DA levels in the nucleus accumbens. However, both drugs increased extracellular 5-HT levels, and noribogaine was more potent in this respect. Results from in vitro experiments indicated that ibogaine and noribogaine interact with 5-HT transporters to inhibit 5-HT uptake. The present findings demonstrate that noribogaine is biologically active and undoubtedly contributes to the in vivo pharmacological profile of ibogaine in rats. Noribogaine is approximately 10 times more potent than ibogaine as an indirect 5-HT agonist. More importantly, noribogaine appears less apt to produce the adverse effects associated with ibogaine, indicating the metabolite may be a safer alternative for medication development.

Drug addiction is a debilitating disease with few treatment options. The severity of the addiction crisis has prompted researchers to explore the plant kingdom as a source of novel therapeutics. An example of a plant-derived compound with potential efficacy in treating drug dependence is the alkaloid ibogaine (Popik et al., 1995). Ibogaine is found in the roots of the African shrub *Tabernanthe iboga*, and psychoactive properties of the drug have been known for decades (Goutarel et al., 1993). More recently, ibogaine has gained a reputation as an "addiction interrupter" based on experimental data from animals and anecdotal reports from addict self-help groups. Single injections of ibogaine reduce drug-seeking behavior in rats previously trained to self-administer cocaine and morphine (Glick et al., 1991, 1994). Ibogaine also alleviates opioid withdrawal symptoms in morphine-dependent rodents (Dzolic et al., 1988; Glick et al., 1992) and heroin-dependent human patients (Sheppard, 1994; Alper et al., 1999).

Despite such promising findings, the mechanisms responsible for the antiaddictive properties of ibogaine are unknown. Radioligand binding studies show that ibogaine binds with low potency (i.e., $IC_{50} = \sim 1\text{--}10\ \mu\text{M}$) to numerous molecular targets in brain tissue, including σ -2 receptors (Bowen et al., 1995; Mach et al., 1995), serotonin (5-HT), and dopamine (DA) transporters (Ser-shen et al., 1992; Mash et al., 1995), κ - and μ -opioid receptors (Deecher et al., 1992; Sweetnam et al., 1995), and NMDA ion channels (Popik et al., 1995). Concentrations of ibogaine in rat brain are 10 to 20 μM after systemic administration of the drug (Hough et al., 1996; Staley et al., 1996), indicating that micromolar-affinity binding sites are functionally relevant in vivo. Determining which particular binding sites are involved in the in vivo actions of ibogaine has proven difficult, and there is speculation that the therapeutic potential of ibogaine is related to coactivation of multiple transmitter systems in the brain (Glick and Maisonneuve, 1998; Mash et al., 1998).

Ibogaine elicits behavioral and neurochemical changes

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ABBREVIATIONS: 5-HT, 5-hydroxytryptamine, serotonin; DA, dopamine; NMDA, N-methyl-D-aspartate; SERT, serotonin transporter; GC/MS, gas chromatography/mass spectroscopy; DAT, dopamine transporter; RTI-55, 3 β -(4-iodophenyl)tropan-2 β -carboxylic acid methyl ester; GBR12935, 1-[2-(diphenylmethoxy)-ethyl]-4-(3-phenylpropyl)piperazine dihydrochloride; GBR12909, 1-(2-[bis(4-fluorophenyl)methoxy]ethyl)-4-[3-phenylpropyl]piperazine dihydrochloride.

that persist for 24 h or more (Glick et al., 1991; Maisonneuve et al., 1992), whereas the drug displays a biological half-life of only a few hours (Dhahir et al., 1971; Zetler et al., 1972). These observations are consistent with the formation of a long-acting ibogaine metabolite (Maisonneuve et al., 1992). Mash and colleagues (Hearn et al., 1995; Mash et al., 1995) were the first to identify a major *o*-desmethyl metabolite of ibogaine, 12-hydroxyibogamine (noribogaine), in the blood and urine from human subjects treated with ibogaine. Recent evidence indicates noribogaine is formed by the action of cytochrome P450 enzymes in the liver (Obach et al., 1998). Interestingly, the *in vitro* pharmacology of noribogaine differs from that of ibogaine, with noribogaine showing greater affinity for 5-HT transporters (SERTs) (Staley et al., 1996) and lower affinity for α -2 receptors (Bowen et al., 1995). Surprisingly, few investigators have systematically evaluated the *in vivo* biological activity of noribogaine (Glick et al., 1996). Thus, the aim of the present experiments was to examine specific behavioral, neuroendocrine, and neurochemical effects of ibogaine and noribogaine in rats.

Materials and Methods

Animals. Adult male Sprague-Dawley rats (Charles River, Wilmington, MA) weighing 350 to 400 g were housed in standard conditions (lights on from 7:00 AM to 7:00 PM) with food and water freely available. Animals were maintained in facilities fully accredited by the American Association of the Accreditation of Laboratory Animal Care, and experiments were performed in accordance with the Institutional Care and Use Committee of the National Institute on Drug Abuse, Intramural Research Program.

Drugs and Reagents. Ibogaine HCl (ibogaine) and 12-hydroxyibogamine HCl (noribogaine) were generously provided by the National Institute on Drug Abuse Drug Supply Program (Rockville, MD). Methoxyflurane (Metofane) was purchased from Pittman-Moore (Phillipsburg, NJ), whereas sodium pentobarbital was obtained from the National Institute on Drug Abuse, Intramural Research Program Pharmacy (Baltimore, MD). Chromatographic reagents, buffer salts, and other chemicals were obtained from Sigma Chemical Co. (St. Louis, MO).

Pharmacokinetic Experiments. Rats were anesthetized with Metofane and indwelling catheters made of Silastic (Dow-Corning, Midland, MI) tubing were surgically implanted into the right jugular vein as previously described (Baumann et al., 1998). After 7 to 10 days of recovery, rats received single injections of ibogaine via the i.p. (40 mg/kg) or i.v. (10 mg/kg) route. Ibogaine was diluted in an ethanol:saline vehicle (1:10) and injected slowly in a volume of 1 ml/kg. Blood samples (0.4 ml) were withdrawn from the catheters immediately before injection and at 1, 2.5, 5, 10, 30, 60, 120, and 180 min, and 24 h after ibogaine treatment. Blood samples were frozen and stored at -70°C until the time of assay by gas chromatography/mass spectroscopy (GC/MS). An equivalent volume of saline was injected into the catheters after each blood draw to maintain volume homeostasis.

Ibogaine and noribogaine were identified by subjecting extracts of blood to full scan electron impact GC/MS on Finnigan 4521 (quadrupole) and Finnigan ITS-40 (ion trap) mass spectrometers (Hearn et al., 1995; Mash et al., 1995). Compound identification was verified by comparing retention times and fragmentation patterns of samples with standards. Samples were solvent extracted using ethyl acetate under basic conditions ($\text{pH} > 10$) with *O*-(D_3 -methyl)-ibogaine as an internal standard and derivatization of noribogaine to a propyl ether. The GC/MS was operated at full scan electron ionization mode scanning from m/z 45 to 450 at 1 s/scan. Ion ratios for molecular ion of ibogaine (m/z 310), and noribogaine propyl ether (m/z 338), to that of *O*-(D_3 -methyl)-ibogaine (m/z 313) were subjected to least-squares

linear regression versus concentration. Standard curves were linear and reproducible, with intra-assay coefficients of variability less than 10%. The lower limit of detection was 5 ng/ml for ibogaine and derivatized noribogaine.

Behavioral and Neuroendocrine Experiments. Rats were anesthetized with Metofane and catheters made of Silastic tubing were implanted into the right jugular vein. After 7 to 10 days of recovery, rats received i.v. ibogaine, noribogaine, or ethanol:saline (1:10) vehicle. Drugs were administered at 1 or 10 mg/kg in a 1-ml/kg volume. Blood samples (0.5 ml) were withdrawn immediately before injection and 15, 30, and 60 min after injection. An equivalent volume of saline was replaced after each blood draw and plasma samples were stored at -70°C . Rats were observed for 90-s intervals at 2, 10, 20, and 30 min after treatment as described previously (Baumann et al., 1998). All observations were carried out by an investigator who was blind to the treatment condition. Specific behaviors were scored using a graded scale: 0, absent; 1, equivocal; 2, present; and 3, intense. Behaviors included horizontal locomotor activity, tremors, forepaw tapping (tapping), penile erections, and chewing movements. Rats were given a single numerical score for each behavior that consisted of the summed total for that behavior across all time points.

Plasma corticosterone levels were assayed by double-antibody radioimmunoassay using commercial kits (ICN Biomedicals Inc., Costa Mesa, CA). Plasma prolactin levels were measured by radioimmunoassay using materials obtained from the National Hormone and Pituitary Program (Rockville, MD) and commercially available ^{125}I -labeled prolactin (Covance Laboratories, Vienna, VA). Assays were conducted as described previously (Baumann et al., 1998). Samples were assayed in duplicate in single assays and average intra-assay coefficients of variability were $<8\%$.

Microdialysis Experiments. Rats were anesthetized with sodium pentobarbital (60 mg/kg i.p.). Intra-accumbens guide cannulae (ML, ± 1.5 mm; AP, $+1.6$ mm from bregma; DV, -6.2 mm from dura) and indwelling jugular catheters were surgically implanted as previously described (Baumann et al., 2000a). After 7 to 10 days of recovery, microdialysis probes (CMA/12; CMA/Microdialysis, Acton, MA) were lowered into guide cannulae and perfused at $0.5 \mu\text{l}/\text{min}$ with Ringers' solution containing 147.0 mM NaCl, 4.0 mM KCl, and 1.8 mM CaCl_2 . On the following morning, dialysate samples were collected at 20-min intervals and assayed for DA and 5-HT by high pressure liquid chromatography with electrochemical detection according to published methods (Baumann et al., 2000a). Once three baseline samples were obtained, rats received i.v. ibogaine, noribogaine, or ethanol:saline (1:10) vehicle. Drugs were administered at 1 or 10 mg/kg in a 1-ml/kg volume. Dialysate samples were collected for 60 min (three samples) after injection.

Aliquots of dialysate ($5 \mu\text{l}$) were injected onto a C18, $3\text{-}\mu\text{m}$ microbore column (SepStik; Bioanalytical Systems, Inc., West Lafayette, IN) that was coupled to an amperometric detector (LC-4C; BAS, West Lafayette, IN) with a working electrode potential of $+700$ mV relative to a Ag/AgCl reference. Mobile phase consisting of 150 mM monochloroacetic acid, 145 mM sodium hydroxide, 1.7 mM sodium octyl sulfate, 0.2 mM Na_2EDTA , 1 ml of triethylamine, 6% MeOH, 6% CH_3CN per liter of H_2O (final pH = 5) was pumped at $60 \mu\text{l}/\text{min}$. A MAXIMA 820 software system (Waters-Millipore, Milford, MA) was used for peak amplification, integration, and analysis. Peak heights of unknowns were compared with peak heights of standards, and the lower limit of assay sensitivity ($3 \times$ baseline) was 100 fg for DA and 5-HT. Data are mean $\pm$ S.E.M. for $N = 7$ to 8 rats/group expressed as percentage of baseline.

5-HT and DA Transporter Binding Assays. The binding of ibogaine and noribogaine to SERT and DA transporters (DAT) was determined in rat caudate using the high-affinity cocaine analog [^{125}I]RTI-55 as the radioligand (Rothman et al., 1994). Rats were euthanized with CO_2 and decapitated. Caudates were dissected and each caudate was placed in 20 ml of ice-cold 55 mM sodium phosphate buffer at pH 7.4 (binding buffer) and homogenized. The ho-

mogenate was centrifuged for 10 min at 30,000g and the pellet was resuspended in 20 ml of binding buffer. The homogenate was recentrifuged and the pellet was resuspended in 10 ml of binding buffer. A 0.5-ml aliquot was saved for protein determination and the remaining homogenate was brought to a final volume of 110 ml (SERT binding) or 220 ml (DAT binding) with ice-cold binding buffer. Polystyrene tubes (12 × 75 mm) were filled with 100 μ l of competing drug, 100 μ l of radioligand, and 50 μ l of blocker. Drugs and blockers were dissolved in binding buffer. [125 I]RTI-55 (100 pM) was made up in a protease inhibitor cocktail that contained 1 mg/ml bovine serum albumin in binding buffer.

The assay was initiated by the addition of 750 μ l of membranes to the tubes. The incubation time was 18 h at 4°C (equilibrium) in a final volume of 1 ml. Competition curves were generated by displacing [125 I]RTI-55 (10 pM final tube concentration) with 8 to 10 concentrations of ibogaine or noribogaine (10 nM–1 mM final tube concentration) in the presence of blockers. Binding to SERT was determined in the presence of 100 nM GBR12935, whereas binding to DAT was determined in the presence of 50 nM paroxetine. Non-specific binding was determined in the presence of 10 μ M GBR12909. Brandel cell harvesters (Biomedical Research and Development, Gaithersburg, MD) were used to filter the samples over Whatman GF/B filters that were presoaked in wash buffer (ice-cold 10 mM Tris pH 7.4 in 150 mM NaCl) that contained 2% polyethylenimine. Samples were first diluted in 4 ml of wash buffer, filtered, and washed with five additional 4-ml aliquots of wash buffer. The 125 I retained on filters was counted in a gamma counter (Micromedic, Huntsville, AL) at 80% efficiency.

[3 H]5-HT and [3 H]DA Uptake Assays. The effect of ibogaine and noribogaine on uptake of [3 H]5-HT and [3 H]DA was evaluated using published methods (Rothman et al., 1993). Rats were euthanized with CO₂ and decapitated. Brains were removed on ice and synaptosomes were prepared from whole brain minus cerebellum for [3 H]5-HT reuptake, or from caudate for [3 H]DA reuptake. Fresh tissue was homogenized in ice-cold 10% sucrose using a Potter-Elvehjem homogenizer. Homogenates were centrifuged at 1000g for 10 min at 4°C and supernatants were retained on ice. Polystyrene tubes (12 × 75 mm) were filled with 50 μ l of Krebs-phosphate buffer consisting of 154 mM NaCl, 2.9 mM KCl, 1.1 mM CaCl₂, 0.8 mM MgCl₂, 5 mM glucose at pH 7.4, with 1 mg/ml ascorbic acid and 50 μ M pargyline added (uptake buffer), 750 μ l of [3 H]transmitter diluted in uptake buffer, and 100 μ l of inhibitor.

The uptake assay was initiated by adding 100 μ l of the synaptosomal preparation to the tubes. Inhibition curves were generated by incubating 3 H transmitter with 8 to 10 concentrations of ibogaine or noribogaine (10 nM–1 mM final tube concentration) diluted in uptake buffer. The 5-HT reuptake experiments were conducted in the presence of 100 nM nomifensine and 100 nM GBR12935 to prevent uptake into norepinephrine or DA nerve terminals. Nonspecific uptake was measured in the presence of 10 μ M fluoxetine for [3 H]5-HT and 1 μ M GBR12909 for [3 H]DA. Incubations of 30 or 15 min were carried out at 25°C for the reuptake of [3 H]5-HT and [3 H]DA, respectively. The incubations were terminated by adding 4 ml of wash buffer containing 10 mM Tris HCl (pH 7.4) in 0.9% NaCl, followed by rapid filtration over Whatman GF/B filters and two additional wash cycles. The tritium retained on the filters was counted in a beta counter at 45% efficiency after an overnight extraction into ICN Cytosint cocktail (ICN Biomedicals Inc.).

Statistical Analyses. Pharmacokinetic data were analyzed using PCNONLIN, a least-squares nonlinear curve-fitting program (SCI Software, Apex, NC). Behavioral effects of drugs were evaluated using one-factor (drug dose) ANOVA. Neuroendocrine and neurochemical effects of ibogaine and noribogaine were analyzed by one-factor (drug dose) ANOVA with repeated measures. When significant *F* values were obtained, a Newman-Keuls post hoc test was used to assess significance between group means. *P* < 0.05 was the minimum criterion for statistical significance. For the uptake and binding assays, the data from three experiments were pooled and fit to

the two-parameter logistic equation for the best-fit estimates of the IC₅₀ and slope factor using MLAB-PC (Civilized Software, Bethesda, MD) as described elsewhere (Rothman et al., 1994).

Results

Pharmacokinetic Experiments. Figure 1 shows the chemical structures of ibogaine and noribogaine. Table 1 summarizes the pharmacokinetic constants for ibogaine and noribogaine measured after administration of ibogaine via the i.p. (40 mg/kg) and i.v. (10 mg/kg) routes. Figure 2 illustrates the time-concentration profiles for ibogaine and noribogaine measured in whole blood after i.p. (Fig. 2A) and i.v. (Fig. 2B) ibogaine administration. Following i.p. injection, circulating levels of ibogaine peaked (*C*_{max}) at 6 min, whereas levels of noribogaine increased slowly to plateau at 144 min postinjection. The half-life of ibogaine (*t*_{1/2}) in the blood was 142 min, or about 2 h, in agreement with previous reports (Dhahir et al., 1971; Zetler et al., 1972). Noribogaine *C*_{max} (7265 ± 953 ng/ml) exceeded that of ibogaine (3859 ± 789 ng/ml) to yield a noribogaine-to-ibogaine *C*_{max} ratio of 1.88. These data demonstrate that a substantial fraction of ibogaine is metabolically converted to noribogaine when ibogaine is given via the i.p. route. Blood levels of ibogaine were nearly undetectable 24 h after i.p. treatment, but blood levels of noribogaine were 308 ± 50 ng/ml. Following i.v. injection, ibogaine levels peaked within 1 min, whereas noribogaine levels increased slowly to a peak at 132 min. In this case, noribogaine *C*_{max} (1198 ± 102 ng/ml) was much less than that of ibogaine (18246 ± 979 ng/ml), giving a noribogaine-to-ibogaine *C*_{max} ratio of 0.07. These data show that a much smaller fraction of ibogaine is converted to noribogaine when ibogaine is administered via the i.v. route. Based on the pharmacokinetic data, we chose to examine the neurobiological effects of ibogaine and noribogaine using the i.v. route of administration because this allowed an assessment of drug-

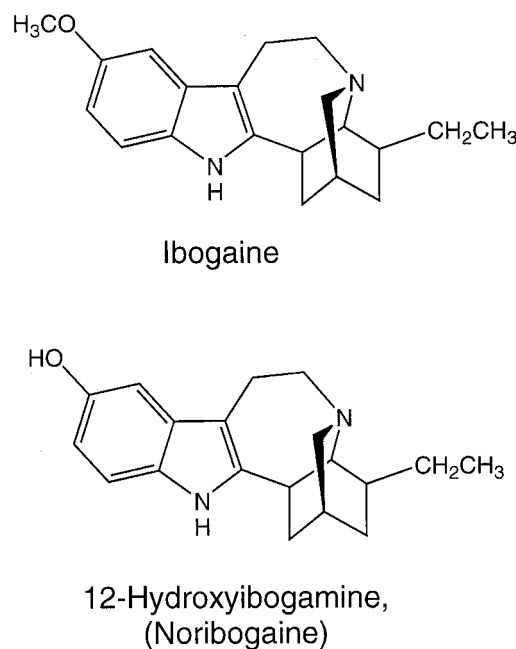


Fig. 1. Chemical structures of ibogaine and 12-hydroxyibogamine (noribogaine).

TABLE 1

Pharmacokinetic constants for ibogaine and noribogaine measured after administration of ibogaine via the i.p. (40 mg/kg) and i.v. (10 mg/kg) routes

Ibogaine was injected at time 0 and serial blood samples were withdrawn at various times thereafter. Whole blood levels of ibogaine and noribogaine were determined using GC/MS (see *Materials and Methods*). Maximal blood levels of each alkaloid (C_{max}), the time at which maximal blood levels were achieved (T_{max}), and the estimated half-life ($t_{1/2}$), were calculated using PCNONLIN noncompartmental analysis algorithm. Values are mean $\pm$ S.E.M. for $N = 6$ rats/group.

Treatment (Dose, Route)	Alkaloid	C_{max} ng/ml	T_{max} min	$t_{1/2}$
Ibogaine (40 mg/kg, i.p.)	Ibogaine	3,859 $\pm$ 789	6.0 $\pm$ 1.7	142.6 $\pm$ 29.7
	Noribogaine	7,265 $\pm$ 953	144.0 $\pm$ 24.0	NQ
Ibogaine (10 mg/kg, i.v.)	Ibogaine	18,246 $\pm$ 979	1.0 $\pm$ 0.1	51.4 $\pm$ 2.7
	Noribogaine	1,198 $\pm$ 102	132.0 $\pm$ 12.0	NQ

NQ, not quantified.

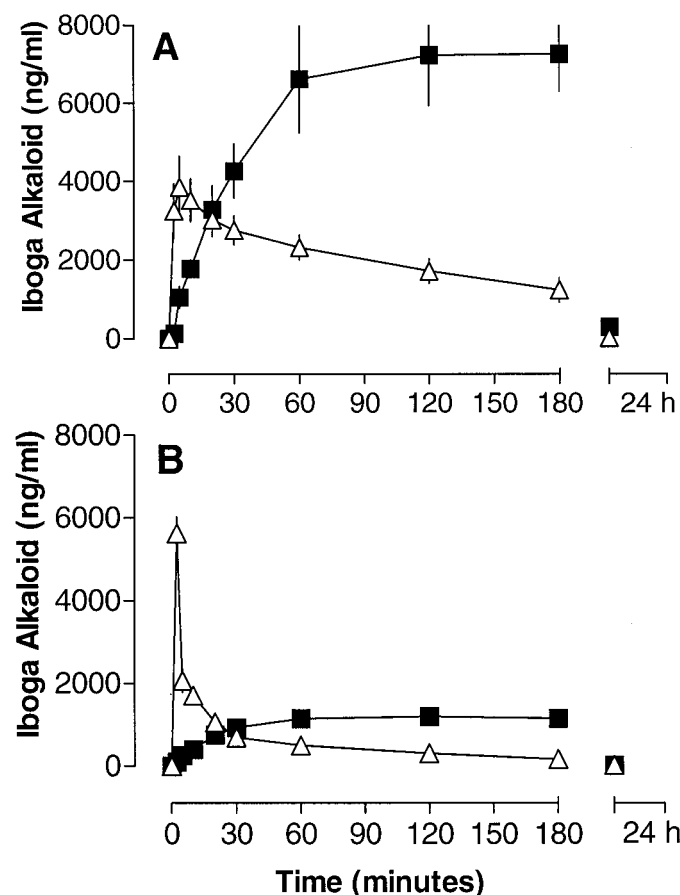


Fig. 2. Time-concentration profiles for ibogaine (Δ) and noribogaine ($\blacksquare$), determined after administration of ibogaine at 40 mg/kg i.p. (A) or 10 mg/kg i.v. (B). Rats received ibogaine injections at time 0 and serial blood samples were withdrawn at various times thereafter. Whole blood levels of ibogaine and noribogaine were determined using GC/MS methods. Data are mean $\pm$ S.E.M. for $N = 6$ rats/group.

induced effects without the complication of significant first-pass metabolism.

Behavioral and Neuroendocrine Experiments. Figure 3 shows the effects of i.v. ibogaine (Fig. 3A) and noribogaine (Fig. 3B) on behaviors in rats. Ibogaine produced a dose-related increase in locomotor activity ($F[2,21] = 5.40$, $P < 0.01$), tremors ($F[2,21] = 19.25$, $P < 0.0001$), forepaw tapping ($F[2,21] = 17.54$, $P < 0.0001$), and chewing movements ($F[2,21] = 5.13$, $P < 0.01$). The ibogaine-induced tremorigenic effect consisted of fine tremors of the face, head, and neck, as well as prominent shivering movements of the trunk. After the highest dose of ibogaine (10 mg/kg), most rats displayed abnormal postures, body sway, and a stagger-

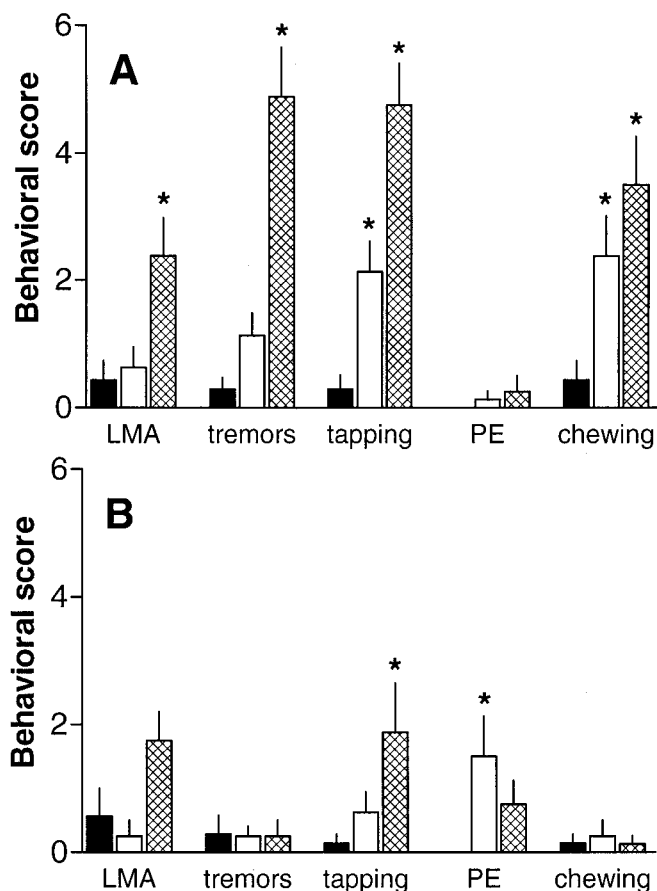


Fig. 3. Effects of ibogaine (A) and noribogaine (B) on behavior. Rats received i.v. injection of either ibogaine, noribogaine, or ethanol:saline (1:10) vehicle at time 0. Vehicle ($\blacksquare$), 1 mg/kg ($\square$), 10 mg/kg ($\hatched$). Behaviors were scored at 2, 10, 20, and 30 min after injection using the graded scale: 0, absent; 1, equivocal; 2, present; and 3, intense. Specific behaviors were horizontal locomotor activity (LMA), tremors, forepaw tapping (tapping), penile erections (PE), and chewing. Rats were given a single numerical score for each behavior that was the summed total across all time points. Data are mean $\pm$ S.E.M. for $N = 8$ rats/group. * $P < 0.05$ with respect to vehicle controls.

ing-type locomotion. In contrast to ibogaine, noribogaine did not elicit tremors, chewing movements, or ataxia. Noribogaine did cause modest locomotor activation ($F[2,21] = 4.36$, $P < 0.02$) and a small increase in forepaw tapping ($F[2,21] = 3.09$, $P < 0.05$) at the highest dose. In addition, noribogaine stimulated an increase in the number of penile erections ($F[2,21] = 2.98$, $P < 0.05$), a behavior that was rarely seen with ibogaine. It should be mentioned that behavioral effects elicited by both drugs were transient, with rats appearing normal by 30 min postinjection.

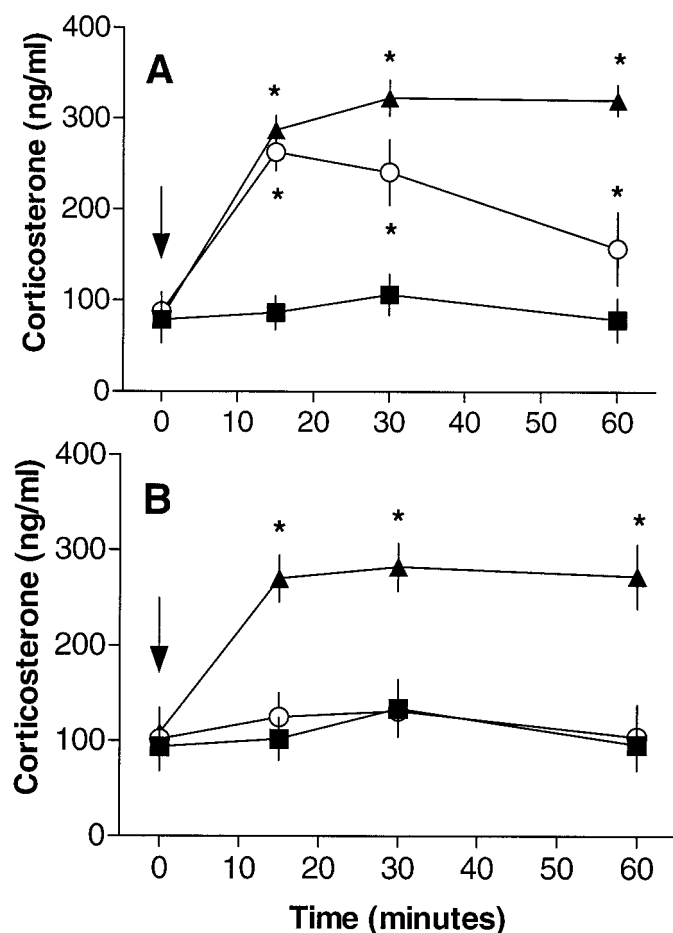


Fig. 4. Effects of ibogaine (A) and noribogaine (B) on plasma corticosterone. Rats received i.v. injection of either drug (1 mg/kg, ○; 10 mg/kg, ▲) or ethanol:saline (1:10) vehicle (■), and serial blood samples were withdrawn. Corticosterone was assayed by radioimmunoassay. Data are mean $\pm$ S.E.M. for $N = 8$ rats/group. * $P < 0.05$ with respect to vehicle controls.

Figure 4 depicts the effects of ibogaine (Fig. 4A) and noribogaine (Fig. 4B) on circulating corticosterone. Plasma corticosterone was significantly increased by both ibogaine ($F[2,21] = 22.63$, $P < 0.0001$) and noribogaine ($F[2,21] = 16.46$, $P < 0.001$). Post hoc tests revealed that ibogaine was more potent than noribogaine in this regard (Newman-Keuls, $P < 0.05$), with 1- and 10-mg/kg doses of ibogaine causing significant and sustained elevations in corticosterone. As shown in Fig. 5, plasma prolactin was increased after ibogaine ($F[2,21] = 6.88$, $P < 0.005$) and noribogaine ($F[2,21] = 44.49$, $P < 0.0001$). The prolactin-releasing action of both drugs was similar, consisting of a transient burst of hormone release after the highest dose.

Microdialysis Experiments. Figure 6 depicts the effects of ibogaine (Fig. 6A) and noribogaine (Fig. 6B) on extracellular levels of DA in rat nucleus accumbens. Injection of vehicle (10% ethanol in saline) did not affect extracellular DA levels over the course of sampling, and dialysate DA was not altered with respect to vehicle by either ibogaine or noribogaine. Figure 7 shows that vehicle injection did not alter extracellular 5-HT levels, but dialysate 5-HT was significantly elevated with respect to vehicle after injection of both ibogaine ($F[2,19] = 48.79$, $P < 0.001$) and noribogaine ($F[2,19] = 28.06$, $P < 0.0001$). Post hoc tests revealed that

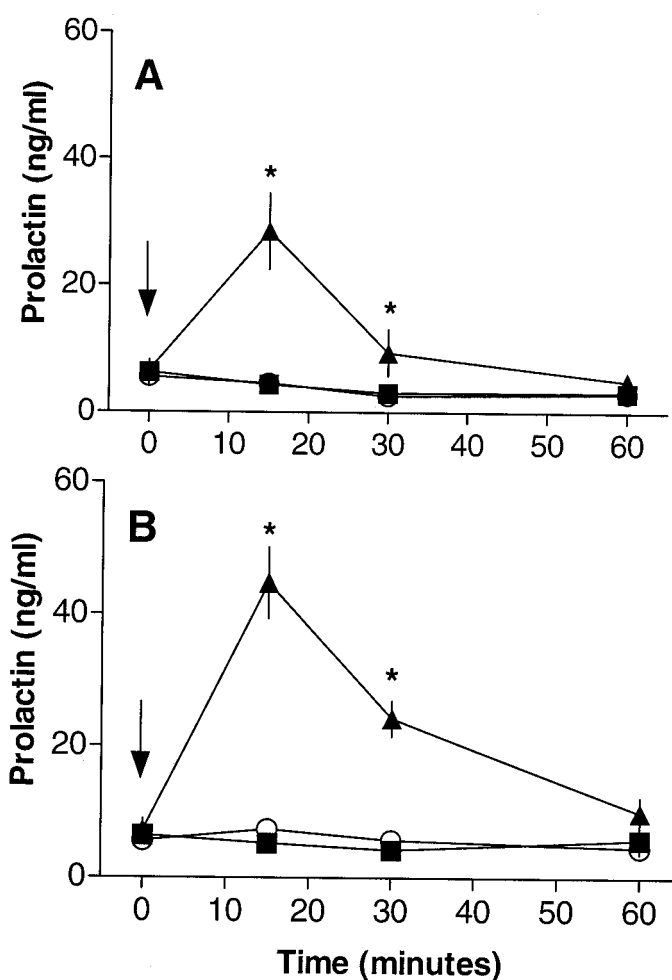


Fig. 5. Effects of ibogaine (A) and noribogaine (B) on plasma prolactin. Rats received i.v. injection of either drug (1 mg/kg, ○; 10 mg/kg, ▲) or ethanol:saline (1:10) vehicle (■), and serial blood samples were withdrawn. Prolactin was assayed by radioimmunoassay. Data are mean $\pm$ S.E.M. for $N = 8$ rats/group. * $P < 0.05$ with respect to vehicle controls.

ibogaine increased 5-HT only after the 10-mg/kg dose, whereas noribogaine stimulated a rise in 5-HT that was significant after 1- and 10-mg/kg doses. Thus, noribogaine was more potent than ibogaine at increasing dialysate 5-HT. The drugs appeared to exhibit similar efficacy since the maximal elevations in 5-HT were 2- to 3-fold for both drugs.

Binding and Uptake Experiments. Table 2 summarizes the effects of ibogaine and noribogaine in assays measuring transporter binding and monoamine uptake. Ibogaine and noribogaine displayed comparable affinities for [125 I]RTI-55-labeled DAT sites, with IC_{50} values of 11.83 ± 0.39 and 4.17 ± 0.19 μ M, respectively. At SERT sites, the potency of noribogaine ($IC_{50} = 0.18 \pm 0.01$ μ M) was 20-times greater than ibogaine ($IC_{50} = 3.85 \pm 0.21$ μ M). In accordance with the binding data, ibogaine and noribogaine were equivalent in their ability to inhibit [3 H]DA uptake with IC_{50} values of 10.03 ± 0.72 and 13.05 ± 0.72 μ M, respectively. In the [3 H]5-HT uptake assay, noribogaine ($IC_{50} = 0.33 \pm 0.02$ μ M) was about 10-fold more potent than ibogaine ($IC_{50} = 3.15 \pm 0.01$ μ M). The relative potencies of the drugs were similar across the transporter binding and uptake assays, yielding binding-to-uptake ratios close to unity. We have previously reported that low binding-to-uptake ratios are characteristic of pure reuptake inhibitors (Rothman et al., 1999).

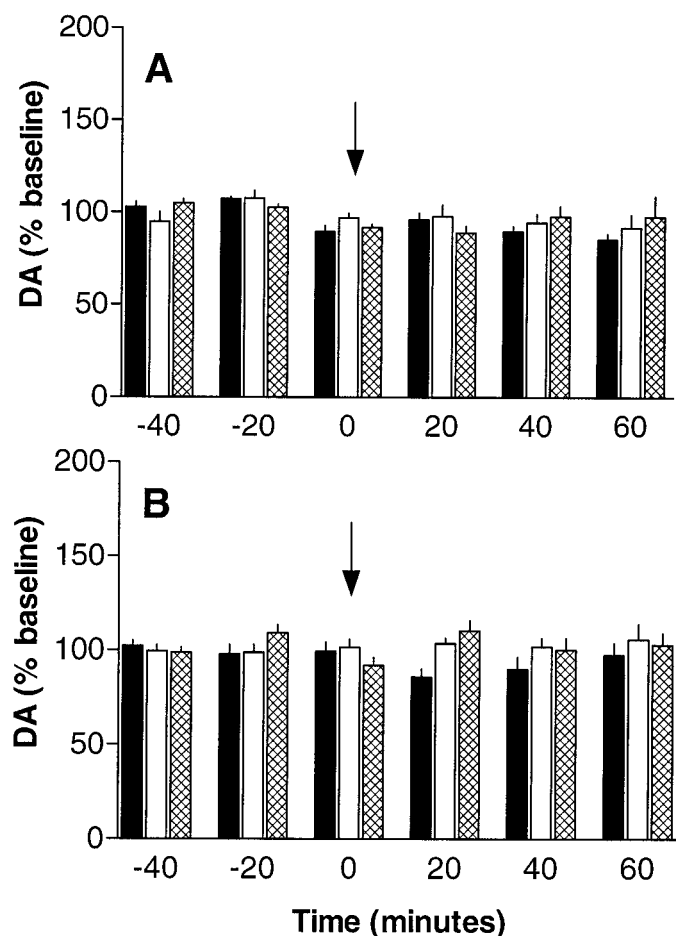


Fig. 6. Effects of ibogaine (A) and noribogaine (B) on extracellular DA in the nucleus accumbens. After three baseline samples were collected, rats received i.v. injection of either drug (1 mg/kg, □; 10 mg/kg, ▨) or ethanol:saline (1:10) vehicle (■). Dialysate samples were collected every 20 min. Data are mean $\pm$ S.E.M. expressed as percentage of baseline for $N = 7$ to 8 rats/group. Baseline levels of DA in dialysate samples from ibogaine and noribogaine groups were 2.65 ± 0.44 and 2.44 ± 0.51 pg/5- μ l sample, respectively.

Discussion

Ibogaine is being evaluated as a potential medication for treating drug dependence, even though the mechanism of ibogaine action is still unresolved (Popik et al., 1995; Glick and Maisonneuve, 1998). It is known that administration of ibogaine to primates leads to formation of a persistent *o*-desmethyl metabolite, noribogaine (Hearn et al., 1995; Mash et al., 1995). The present pharmacokinetic data show that noribogaine is also formed in rats after i.p. and i.v. ibogaine administration, and these data support the work of others (Staley et al., 1996; Pearl et al., 1997). We observed that the ratio of noribogaine to ibogaine in the bloodstream was much higher when ibogaine was injected by the i.p. route rather than the i.v. route. This finding is consistent with the conversion of ibogaine to noribogaine via first-pass metabolism in the liver, as previously reported (Mash et al., 1998; Obach et al., 1998). Biodistribution studies have shown that ibogaine and noribogaine readily penetrate the blood-brain barrier, and indeed these alkaloids achieve much higher concentrations in brain tissue compared with plasma (Staley et al., 1996; Zubaran et al., 1999). Few studies have evaluated the

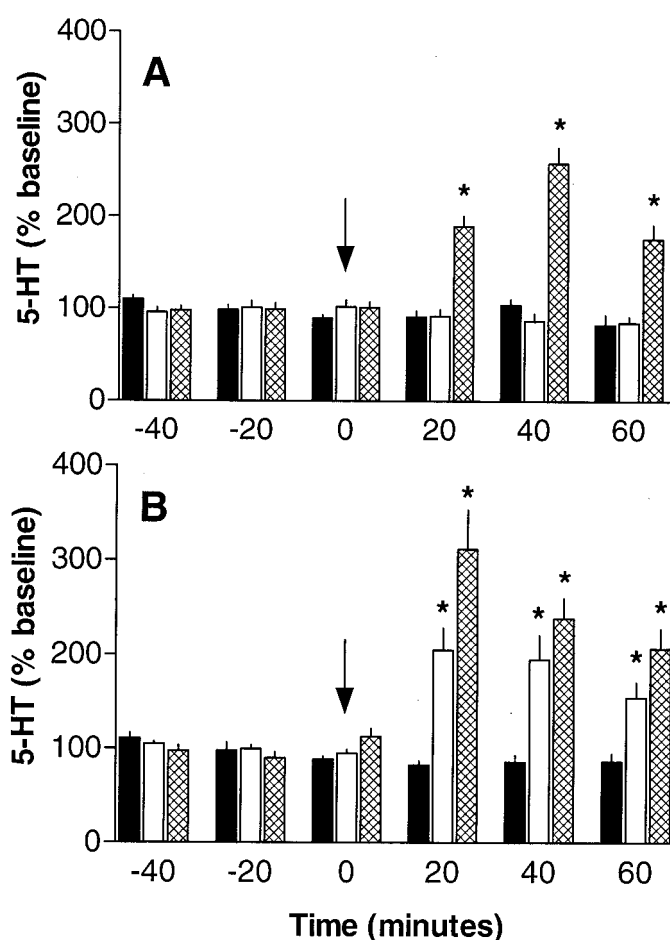


Fig. 7. Effects of ibogaine (A) and noribogaine (B) on extracellular 5-HT in the nucleus accumbens. After three baseline samples were collected, rats received i.v. injection of either drug (1 mg/kg, □; 10 mg/kg, ▨) or ethanol:saline (1:10) vehicle (■). Dialysate samples were collected every 20 min. Data are mean $\pm$ S.E.M. expressed as percentage of baseline for $N = 7$ to 8 rats/group. Baseline levels of 5-HT in dialysate samples from ibogaine and noribogaine groups were 0.41 ± 0.08 and 0.38 ± 0.07 pg/5- μ l sample, respectively. * $P < 0.05$ with respect to the mean response for saline-treated rats.

TABLE 2

Inhibitory potency of ibogaine and noribogaine in assays of transporter binding and monoamine uptake in rat brain tissue

Values are mean $\pm$ S.D. expressed as IC_{50} values determined from three independent experiments each performed in triplicate. Binding assays used [125 I]RTI-55 to label DAT and SERT sites in rat caudate. DAT binding was conducted in the presence of 50 nM paroxetine, whereas SERT binding was conducted in the presence of 100 nM GBR12935. Uptake assays were performed in synaptosomes prepared from whole rat brain minus cerebellum for [3 H]5-HT and rat caudate for [3 H]DA. See *Materials and Methods* for details.

Assay	Ibogaine IC_{50}	Noribogaine IC_{50}
	μ M	
[125 I]RTI-55-labeled DAT	11.83 ± 0.39	4.17 ± 0.19
[125 I]RTI-55-labeled SERT	3.85 ± 0.21	0.18 ± 0.01
[3 H]DA uptake	10.03 ± 0.72	13.05 ± 0.72
[3 H]5-HT uptake	3.15 ± 0.10	0.33 ± 0.02

in vivo neurobiological activity of noribogaine (Glick et al., 1996). Therefore, a major aim of the present study was to compare the behavioral, neuroendocrine, and neurochemical effects of ibogaine and noribogaine in rats. The i.v. route of drug administration was used to minimize the effects of first-pass metabolism.

Ibogaine produced a range of behaviors that included tremors, forepaw tapping, and impaired coordination. Our results are consistent with prior reports showing ibogaine elicits tremors and ataxia when administered to rats at i.p. doses ranging from 40 to 100 mg/kg (Glick et al., 1992; O'Hearn and Molliver, 1993, 1994). Interestingly, noribogaine did not produce tremors or ataxia, but did increase the incidence of penile erections. Glick et al. (1996) demonstrated that noribogaine is not tremorigenic when administered to female rats. Thus, ibogaine and noribogaine evoke very different behavioral effects despite having similar chemical structures.

It might be assumed that ibogaine-induced behaviors are mediated by central 5-HT mechanisms because tremors and forepaw tapping are hallmark signs of the 5-HT behavioral syndrome (Jacobs, 1976). Ibogaine and 5-HT display chemical similarities as well, since both molecules contain an indole as part of their structure. Irrespective of such similarities, however, the present data indicate that 5-HT mechanisms may not be involved in the locomotor effects of ibogaine. Our microdialysis data, for example, show that noribogaine is more potent than ibogaine in its ability to elevate extracellular 5-HT in the brain. Accordingly, noribogaine has higher affinity for SERT and greater potency at blocking 5-HT uptake compared with ibogaine. Thus, noribogaine is more potent than ibogaine as an indirect 5-HT agonist, yet the metabolite does not elicit tremors or robust forepaw tapping. It is tempting to speculate that σ - and/or NMDA receptors may mediate the adverse behavioral effects of ibogaine because noribogaine displays lower potency at these sites (Bowen et al., 1995; Staley et al., 1996). Similar to ibogaine, drugs that interact with σ - or NMDA sites are known to cause forepaw tapping and ataxia (Hiramatsu et al., 1989).

Ibogaine and noribogaine stimulate the secretion of corticosterone from the adrenal cortex and prolactin from the anterior pituitary. Although ibogaine was a more potent stimulator of corticosterone secretion, the two drugs caused analogous increases in plasma prolactin. The drug-induced hormonal effects reported here are likely mediated via central mechanisms because i.c.v. administration of ibogaine to rats causes elevations in circulating corticosterone and prolactin (M. H. Baumann, unpublished data). In a previous article, we proposed that neuroendocrine effects of ibogaine involve 5-HT mechanisms based on similarities between ibogaine and the 5-HT releaser fenfluramine (Ali et al., 1996). However, it seems doubtful that 5-HT neurons are major contributors to ibogaine-induced corticosterone secretion because ibogaine is less potent than noribogaine at increasing extracellular 5-HT, but more potent as a stimulator of corticosterone. The mechanism responsible for prolactin secretion elicited by ibogaine and noribogaine is not known, but may involve hypothalamic DA neurons (Baumann et al., 2000b). Further studies are needed to determine the specific receptor sites involved in mediating the neuroendocrine actions of iboga alkaloids.

Neither ibogaine nor its metabolite significantly altered extracellular DA levels in the nucleus accumbens. Our in vivo neurochemical data are consistent with previous microdialysis and voltammetry studies showing ibogaine has little or no effect on extracellular DA in rat nucleus accumbens (Maisonneuve et al., 1991; Broderick et al., 1994; Mash et al.,

1995). On the other hand, our results differ from the findings of Glick and coworkers (Glick et al., 1996; Glick and Maisonneuve, 1998) who reported that ibogaine and noribogaine (40 mg/kg i.p.) cause significant *decreases* in dialysate DA levels in rat brain. The reasons for such discrepancies are unclear but may be related to differences in experimental design and methods between studies. For instance, we used i.v. drug administration in male rats, whereas Glick et al. (1996) used i.p. administration in female rats. In any event, the microdialysis findings reported here and elsewhere are surprising given that iboga alkaloids interact with DAT sites to block DA uptake in vitro (Table 2; Wells et al., 1999). Ibogaine and noribogaine inhibit binding to [125 I]RTI-55-labeled DAT sites with IC₅₀ values of 11.83 and 4.17 μ M, respectively. These IC₅₀ values are very similar to those reported by Staley et al. (1996) who used [125 I]RTI-121 to label DAT sites in human striatal tissue. It is well established that acute ibogaine administration to rats causes dramatic, albeit transient, depletion (>50%) of tissue DA in the brain (Maisonneuve et al., 1992; Ali et al., 1996). Collectively, the available data indicate that ibogaine-induced DA depletions are not accompanied by elevations of synaptic DA secondary to DA reuptake blockade.

In the present study, ibogaine and noribogaine interacted at SERT sites to block 5-HT uptake in vitro. We demonstrated that ibogaine and noribogaine inhibit [125 I]RTI-55-labeled SERT binding with IC₅₀ values of 3.85 and 0.18 μ M, respectively. These IC₅₀ values are somewhat higher than those reported by Mash et al. (1995) and Staley et al. (1996) who examined SERT binding in human brain. Nonetheless, all of the data agree that noribogaine is at least 10 times more potent than ibogaine with respect to SERT binding activity. Consistent with the in vitro data, both ibogaine and noribogaine produced a dose-related rise in extracellular 5-HT levels in the nucleus accumbens, with noribogaine being more potent in this regard. Ibogaine and noribogaine appeared to display similar efficacy in their ability to elevate dialysate 5-HT since the maximal effect of both drugs was comparable (i.e., 2- to 3-fold). Based on our radioligand binding data, 5-HT uptake data, and microdialysis data, we hypothesize that ibogaine and noribogaine are 5-HT reuptake inhibitors with a mechanism of action similar to fluoxetine (Gundlach et al., 1997).

The ibogaine-induced elevations in dialysate 5-HT that we report here are analogous to the findings of Broderick et al. (1994) who showed ibogaine (40 mg/kg i.p.) produces a modest rise in extracellular 5-HT in the brain as measured by in vivo microvoltammetry. In contrast, our 5-HT data do not agree with the findings of Wei et al. (1998) who reported that ibogaine and noribogaine cause marked elevations in dialysate 5-HT in rat nucleus accumbens. In the Wei et al. (1998) study, i.p. ibogaine (40 mg/kg) elicited a 25-fold increase in extracellular 5-HT, whereas an equivalent dose of noribogaine caused an 8-fold increase. Interestingly, the same study showed that i.v. ibogaine (10 mg/kg) stimulated a 3-fold rise in dialysate 5-HT analogous to the effect of i.v. ibogaine reported here. The authors concluded that ibogaine is a 5-HT releaser, whereas noribogaine is a 5-HT uptake inhibitor.

There are several caveats related to the 5-HT data reported by Wei et al. (1998) that deserve comment. First, only one dose of drug was tested in their study precluding deter-

mination of dose-response effects. Second, we (Rothman et al., 1999) have administered very high doses of 5-HT-releasing agents such as fenfluramine and rarely observe such large (i.e., 25-fold) elevations in extracellular 5-HT. Finally, the results of Wei et al. (1998) are difficult to reconcile with the present pharmacokinetic findings where maximal blood levels of ibogaine were $3,859 \pm 789$ ng/ml after i.p. injection (40 mg/kg) and $18,247 \pm 987$ ng/ml after i.v. injection (10 mg/kg). Stated more simply, it seems improbable that i.p. ibogaine could produce greater effects than i.v. ibogaine when blood levels (and presumably brain levels) of the drug are significantly lower after i.p. dosing. One possibility that might explain these discrepancies is that an unidentified metabolite of ibogaine is formed after i.p. injection, and this metabolite is a very powerful 5-HT-releasing agent.

In summary, we have shown that ibogaine is converted to its *o*-desmethyl metabolite, noribogaine, in rats. Maximal concentrations of noribogaine in blood actually exceed those of the parent compound when ibogaine is administered via the i.p. route. It seems probable therefore that noribogaine contributes significantly to the in vivo pharmacological actions of ibogaine. Despite their similar chemical structures, ibogaine and noribogaine exhibit differences in their pharmacology. For example, ibogaine elicits tremors and ataxia, whereas noribogaine does not. Ibogaine is more potent than noribogaine as a stimulator of the hypothalamic-pituitary-adrenal axis. Although both alkaloids increase extracellular 5-HT in the brain by a mechanism involving SERT, noribogaine is more potent in this respect. It is well established that 5-HT reuptake inhibitors such as fluoxetine can be effective medications for a variety of psychiatric disorders that often accompany drug addiction (Miller and Guttman, 1997; Baumann and Rothman, 1998), and the serotonergic activity of iboga alkaloids may contribute to their therapeutic potential. Recent evidence indicates that ibogaine and noribogaine display similar antiaddictive properties (Glick et al., 1996; Glick and Maisonneuve, 1998). Based on the present findings, it seems that noribogaine could be a safer, and possibly more efficacious, alternative to ibogaine as a medication for treating substance use disorders.

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References

- Ali SF, Newport GD, Slikker W Jr, Rothman RB and Baumann MH (1996) Neuroendocrine and neurochemical effects of acute ibogaine administration: a time course evaluation. *Brain Res* **737**:215–220.
- Alper KR, Lotsof HS, Frenken GM, Luciano DJ and Bastiaans J (1999) Treatment of acute opioid withdrawal with ibogaine. *Am J Addict* **8**:234–242.
- Baumann MH, Ayestas MA and Rothman RB (1998) Functional consequences of central serotonin depletion produced by repeated fenfluramine administration in rats. *J Neurosci* **18**:9069–9077.
- Baumann MH and Rothman RB (1998) Serotonergic dysfunction during cocaine withdrawal: implications for cocaine-induced depression. In *Drug Abuse Handbook* (Karch SB ed) pp 463–484. CRC Press, Boca Raton, FL.
- Baumann MH, Ayestas MA, Dersch CM and Rothman RB (2000a) Effects of phentermine and fenfluramine on extracellular dopamine and serotonin in rat nucleus accumbens: therapeutic implications. *Synapse* **36**:102–113.
- Baumann MH, Rothman RB and Ali SF (2000b) Comparative neurobiological effects of ibogaine and MK-801 in rats. *Drug Alcohol Depend* **59**:143–151.
- Bowen WD, Vilner BJ, Williams W, Bertha CM, Kuehne ME and Jacobson AE (1995) Ibogaine and its congeners are sigma-2 receptor-selective ligands with moderate affinity. *Eur J Pharmacol* **279**:R1–R3.
- Broderick PA, Phelan FT, Eng F and Wechsler RT (1994) Ibogaine modulates cocaine responses which are altered due to environmental habituation: in vivo microdialysis and behavioral studies. *Pharmacol Biochem Behav* **49**:711–728.
- Deecher DC, Teitler M, Sonderlund DM, Bornmann WG, Kuehne ME and Glick SD (1992) Mechanisms of action of ibogaine and harmaline congeners based on radioligand binding studies. *Brain Res* **571**:242–247.
- Dhahir HI, Jain NC and Forney RB (1971) Methods for detection and determination of ibogaine in biological materials. *J Forensic Sci* **16**:103–108.
- Dzolic ED, Kaplan CD and Dzolic MR (1988) Effect of ibogaine on naloxone precipitated withdrawal in chronic morphine-dependent rats. *Arch Int Pharmacodyn* **294**:64–70.
- Glick SD, Rossman K, Steindorf S and Carlson JN (1991) Effects and after effects of ibogaine on morphine self-administration in rats. *Eur J Pharmacol* **195**:341–345.
- Glick SD, Rossman K, Rao NC, Maisonneuve IM and Carlson JN (1992) Effects of ibogaine on acute signs of morphine withdrawal in rats: independence from tremor. *Neuropharmacology* **31**:497–500.
- Glick SD, Kuehne ME, Raucci J, Wilson TE, Keller RW and Carlson JN (1994) Effects of iboga alkaloids on morphine and cocaine self-administration in rats: relationship to tremorigenic effects and to effects on dopamine release in the nucleus accumbens and striatum. *Brain Res* **657**:14–22.
- Glick SD and Maisonneuve IM (1998) Mechanisms of antiaddictive actions of ibogaine. *Ann NY Acad Sci* **844**:214–226.
- Glick SD, Pearl SM, Cai J and Maisonneuve IM (1996) Ibogaine-like effects of noribogaine in rats. *Brain Res* **713**:294–297.
- Goutarel R, Gollnhoffer O and Sillans R (1993) Pharmacodynamics and therapeutic applications of iboga and ibogaine. *Psychiatric Monographs* **6**:71–111.
- Gundlach C, Martin KF, Heal DJ and Auerbach SB (1997) In vivo criteria to differentiate monoamine reuptake inhibitors from releasing agents: sibutramine is a reuptake inhibitor. *J Pharmacol Exp Ther* **283**:581–591.
- Hearn WL, Pablo J, Hime GW and Mash DC (1995) Identification and quantification of ibogaine and an *o*-demethylated metabolite in brain and biological fluids using gas chromatography-mass spectroscopy. *J Anal Toxicol* **19**:427–434.
- Hiramatsu M, Cho AK and Nabeshima T (1989) Comparison of the behavioral and biochemical effects of the NMDA receptor antagonists, MK-801 and phencyclidine. *Eur J Pharmacol* **166**:359–366.
- Hough LB, Pearl SM and Glick SD (1996) Tissue distribution of ibogaine after intraperitoneal and subcutaneous administration. *Life Sci* **45**:599–606.
- Jacobs BL (1976) Minireview: an animal behavior model for studying central serotonergic synapses. *Life Sci* **19**:777–786.
- Mach RH, Smith CR and Childers SR (1995) Ibogaine possesses a selective affinity for sigma-2 receptors. *Life Sci* **57**:PL57–PL62.
- Maisonneuve IM, Keller RW and Glick SD (1991) Interactions between ibogaine, a potential anti-addictive agent, and morphine: an in vivo microdialysis study. *Eur J Pharmacol* **199**:35–42.
- Maisonneuve IM, Rossman KL, Keller RW and Glick SD (1992) Acute and prolonged effects of ibogaine on brain dopamine metabolism and morphine-induced locomotor activity in rats. *Brain Res* **575**:69–73.
- Mash DC, Kovera CA, Buck BE, Norenberg MD, Shapshak P, Hearn WL and Sanchez-Ramos J (1998) Medication development of ibogaine as a pharmacotherapy for drug dependence. *Ann NY Acad Sci* **844**:274–292.
- Mash DC, Staley JK, Baumann MH, Rothman RB and Hearn WL (1995) Identification of a primary metabolite of ibogaine that targets serotonin transporters and elevates serotonin. *Life Sci* **57**:PL45–PL50.
- Miller NS and Guttman JC (1997) The integration of pharmacological therapy for comorbid psychiatric and addictive disorders. *J Psychoactive Drugs* **29**:249–254.
- Obach RS, Pablo JP and Mash DC (1998) Cytochrome P450D6 catalyzes *O*-demethylation of the psychoactive alkaloid ibogaine to 12-hydroxyibogamine. *Drug Metab Dispos* **26**:764–768.
- O'Hearn E and Molliver ME (1993) Degeneration of Purkinje cells in parasagittal zones of the cerebellar vermis after ibogaine or harmaline. *Neuroscience* **55**:303–310.
- Pearl SM, Hough LB, Boyd DL and Glick SD (1997) Sex differences in ibogaine antagonism of morphine-induced locomotor activity and in ibogaine brain levels and metabolism. *Pharmacol Biochem Behav* **57**:809–815.
- Popik P, Layer RT and Skolnick P (1995) 100 years of ibogaine: neurochemical and pharmacological actions of a putative anti-addictive drug. *Pharmacol Rev* **47**:235–253.
- Rothman RB, Ayestas MA, Dersch CM and Baumann MH (1999) Aminorex, fenfluramine, and chlorphentermine are serotonin transporter substrates: implications for primary pulmonary hypertension. *Circulation* **100**:869–875.
- Rothman RB, Cadet JL, Akunne HC, Silverthorn ML, Baumann MH, Carroll FI, Rice KC, de Costa BR, Partilla JS, Wang JB, et al. (1994) Studies of the biogenic amine transporters. IV. Demonstration of a multiplicity of binding sites in rat caudate membranes for the cocaine analog [125I]RTI-55. *J Pharmacol Exp Ther* **270**:296–309.
- Rothman RB, Lewis B, Dersch CM, Xu H, Radesca L, de Costa BR, Rice KC, Kilburn RB, Akunne HC and Pert A (1993) Identification of a GBR12935 homolog, LR1111, which is over 4000-fold selective for the dopamine transporter, relative to serotonin and norepinephrine transporters. *Synapse* **14**:34–39.
- Sershen H, Hashim A, Harsing L and Lajtha A (1992) Ibogaine antagonizes cocaine-induced locomotor stimulation in mice. *Life Sci* **50**:1079–1086.
- Sheppard SG (1994) A preliminary investigation of ibogaine: case reports and recommendations for further study. *J Subst Abuse Treat* **11**:379–385.
- Staley JK, Ouyang Q, Pablo JP, Hearn WL, Flynn DD, Rothman RB, Rice KC and Mash DC (1996) Pharmacological screen for activities of 12-hydroxyibogamine: a primary metabolite of the indole alkaloid ibogaine. *Psychopharmacology* **127**:10–18.
- Sweetnam PM, Lancaster J, Snowman A, Collins J, Perschke S, Bauer C and Ferkany J (1995) Receptor binding profile suggests multiple mechanisms of action

- are responsible for ibogaine's putative anti-addictive activity. *Psychopharmacology* **118**:369–376.
- Wei D, Maisonneuve IM, Kuehne ME and Glick SD (1998) Acute iboga alkaloid effects on extracellular serotonin (5-HT) levels in nucleus accumbens and striatum in rats. *Brain Res* **800**:260–268.
- Wells GB, Lopez MC and Tanaka JC (1999) The effects of ibogaine on dopamine and serotonin transport in rat brain synaptosomes. *Brain Res Bull* **48**:641–647.
- Zetler G, Singbartl G and Schlosser L (1972) Cerebral pharmacokinetics of tremor-producing harmala and iboga alkaloids. *Pharmacology* **7**:237–248.
- Zubaran C, Shoaib M, Stoleran IP, Pablo J and Mash DC (1999) Noribogaine generalization to the ibogaine stimulus: correlation with noribogaine concentration in rat brain. *Neuropsychopharmacology* **21**:119–126.

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